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Blood Pressure-Lowering Therapy

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Blood Pressure-Lowering Therapy

Isabella Sudano, Elena Osto, and Frank Ruschitzka

Contents

Abstract

Extensive evidence demonstrates that lowering blood pressure can substantially reduce the risk of atherosclerotic cardiovascular disease and death.

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In light of the latest 2018 European Society of Cardiology/European Society of Hypertension Joint Guidelines, we summarize the current recommendations about lifestyle intervention strategies, pharmacotherapy, and device-based treatments for the management of arterial hypertension. Special attention is given to direct effects exerted by some antihypertensive drugs targeting vascular wall cell components that are involved in the pathogenesis of atherosclerosis.

Keywords

Blood pressure medical treatment · Cardiovascular risk factors · Device therapy · Hypertension · Hypertension-driven atherosclerotic complications · Lifestyle interventions

Abbreviations

ACE	Angiotensin-converting enzyme
Ang II	Angiotensin II
ARBs	Angiotensin II receptor blockers
BP	Blood pressure
CCBs	Calcium channel blockers
CVD	Cardiovascular disease
ESC	European Society of Cardiology
ESH	European Society of Hypertension
MR	Mineralocorticoid receptor
NO	Nitric oxide
ROS	Reactive oxygen species
SHF	Swiss Heart Foundation
SNSF	Swiss National Science Foundation

1 Introduction

Continuous progress in understanding the epidemiology, pathophysiology, and pharmacology of arterial hypertension has consistently improved the possibility of an efficient and safe treatment of elevated blood pressure (BP).

Extensive evidence demonstrates that lowering BP can substantially reduce the risk of cardiovascular disease (CVD) and death with similar proportional reductions across various population subgroups. Every 10 mmHg systolic BP reduction significantly diminished the risk of major CVD events (RR 0.80, 95% CI 0.77–0.83), coronary heart disease (0.83, 0.78–0.88), stroke (0.73, 0.68–0.77), heart failure (0.72, 0.67–0.78), and all-cause mortality (0.87, 0.84–0.91) (Ettehad et al. 2016).

Arterial hypertension is characterized by structural and functional changes in blood vessels, which lead to increased arterial stiffness, vascular inflammation, endothelial dysfunction, fatty streaks, early atherosclerotic plaque, plaque progression, and plaque rapture. Vice versa, arterial stiffness, endothelial dysfunction, and vascular inflammation may also contribute to increased BP. Several lifestyle

Table 1 From ESC/ESH guidelines for hypertension, Eur Heart Journal 2018 (©ESC/ESH 2018)

Table 3. Classification of office blood pressure[a] and definitions of hypertension grade[b]			
Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–170	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

BP blood pressure, *SBP* systolic blood pressure
The same classification is used for all ages from 16 years
[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated

interventions and drugs lowering BP were demonstrated to improve endothelial function, decrease arterial stiffness and vascular inflammation, and ultimately prevent the development and/or progression of atherothrombosis.

After exclusion of the main causes of a secondary hypertension, lifestyle modifications should be suggested as BP and cardiovascular risk lowering strategy to every patient with arterial hypertension. However, sooner or later, most patients diagnosed with arterial hypertension will require a pharmacological therapy.

According to the 2018 ESC/ESH Guidelines (Williams et al. 2018), the necessity of a pharmacological therapy will be defined by the grade of arterial hypertension (see Table 1), the cardiovascular risk, and the presence of hypertension-mediated organ damage or concomitant diseases such as a history of cardiovascular events, diabetes mellitus, or chronic kidney disease. The 2018 Guidelines suggest as general rule to reduce office BP below 140/90 mmHg aiming to reach a BP around 130/80 mmHg; see Table 1.

The ultimate goal of antihypertensive therapy is the prevention of cardiovascular events. The higher the absolute cardiovascular risk, the more likely it is that a patient will benefit from a more aggressive BP goal. However, although cardiovascular events generally decrease with more intensive lowering of BP, the risk of adverse effects, cost, and patient inconvenience increase as more medication is added (Ettehad et al. 2016; Williams et al. 2018). See Fig. 1.

This recommendation together with good clinical judgment and shared decision-making between patients and care providers should guide our BP-lowering therapy.

2 Non-pharmacological Therapy

Treatment of hypertension should always include non-pharmacological therapy (Fig. 1) (Williams et al. 2018).

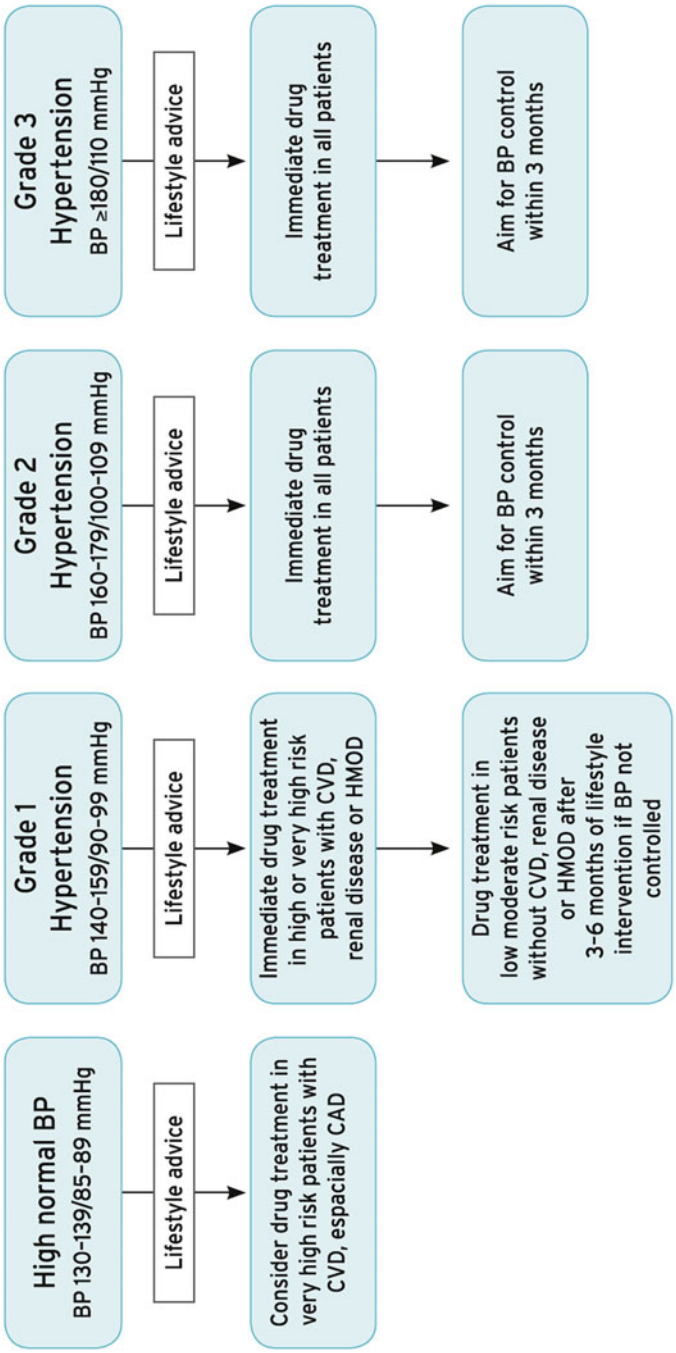

Fig. 1 From ESC/ESH guidelines for hypertension, Eur Heart Journal 2018 (©ESC/ESH 2018)

The ESC/ESH Guidelines (Williams et al. 2018) suggested the following lifestyle changes as contributors for reducing BP and cardiovascular risk to the majority of patients with arterial hypertension: healthy diet including dietary sodium restriction and moderation of alcohol consumption, overweight reduction, regular physical activity, and cessation of consumption of any product containing tobacco or nicotine.

2.1 Salt Restriction

In general, a healthy diet should avoid any excess: moderate sodium reduction is associated with a decrease in BP in hypertensive and normotensive individuals of a maximum of 4.8–2.5 mmHg systolic and 1.9–1.1 mmHg diastolic, respectively (He and MacGregor 2003).

Young patients with hypertension usually are salt-resistant, while older patients as well as obese individuals or patients with diabetes mellitus and chronic kidney disease are characterized by increased salt sensitivity (Weinberger 1996).

Evidence supporting very strong reduction of salt intake is weak. The effect of reduced dietary sodium on cardiovascular event rates remains unclear (Bibbins-Domingo et al. 2010; He et al. 2011; He and MacGregor 2011; Taylor et al. 2011).

Prospective cohort studies have reported an overall increased risk of mortality and cardiovascular events on high sodium intake, but to date, no prospective randomized controlled trial has provided definitive evidence about the optimal sodium intake to minimize cardiovascular events and mortality. However, it was reported that reducing sodium intake below 3 g of sodium per day further reduced BP, but paradoxically was associated with an increased risk of all-cause and cardiovascular mortalities in both the general population and in hypertensive patients, suggesting a J-curve phenomenon (Mente et al. 2016).

Increased potassium intake is associated with BP reduction and may have a protective effect, thereby modifying the association between sodium intake, BP, and CVD. Increasing potassium intake (e.g., including high intake of vegetables and fruits in the diet) could be a problem in patients with diabetes and chronic kidney disease and cannot be applied to all hypertensive patients (Bernabe-Ortiz et al. 2020; Binia et al. 2015; Mente et al. 2016; Miller et al. 2016).

Therefore, every patient with arterial hypertension independently of his/her sodium sensitivity should reduce the sodium consumption and avoid processed and frozen food, which frequently is rich in salt.

2.2 Reduce Alcohol Intake

For a long time, positive linear associations between alcohol consumption, BP, prevalence of hypertension, and cardiovascular risk have been established.

The Prevention and Treatment of Hypertension Study (PATHS) investigated the effects of reduced alcohol consumption on BP; the intervention group had a modest

1.2/0.7 mmHg lower BP than the control group at the end of the 6-month follow-up period. A meta-analysis of 56 epidemiological studies suggested that reduction of alcohol consumption, even for light-moderate drinkers, might be beneficial for cardiovascular health (Holmes et al. 2014). Binge drinking can cause strong increases of BP (Mancia et al. 2013).

Hypertensive men and women, who drink alcohol, should be advised to limit their consumption to 14 units and 8 units per week, respectively (one unit is equal to 125 mL of wine or 250 mL of beer). Alcohol-free days during the week and avoidance of binge drinking are also recommended (Williams et al. 2018).

2.3 Weight Loss and Avoidance of Overweight and Obesity

Weight loss in overweight or obese individuals leads to a significant reduction in BP, independently of exercise and dietary sodium restriction (Appel et al. 2006; Cohen and Gadde 2019), and has multiple beneficial effects against pathologic factors leading to high BP and to end-organ damage in this patient population (Cohen and Gadde 2019).

Weight loss is associated with decreased intra-abdominal pressure exerted on vessels by the excessive visceral fat deposition. Another beneficial effect of weight loss is the amelioration of insulin resistance, which is associated with renal sodium reabsorption and increased sympathetic tone in obesity. Moreover, chronic inflammation associated with overweight/obesity promotes vascular aging, favoring the onset of hypertension. Inflammation also contributes to arterial stiffness and impairs the physiologic anti-contractile effect of perivascular adipocytes on adjacent small arteries (Virdis et al. 2015; Aghamohammadzadeh et al. 2013). Decrease in body weight with lifestyle management, although effective in the short term, is difficult to sustain in the longer-term follow-up. Indeed, the overall efficacy of lifestyle interventions in reducing cardiovascular outcomes has been questioned by the results of the Action for Health in Diabetes (Look AHEAD) Study (Look, Ahead Research Group et al. 2013; Semlitsch et al. 2016). Currently, the most effective pharmacological treatments against obesity include glucagon like peptide-1 (GLP-1) receptor agonists and bariatric surgery. GLP-1 receptor agonists, in particular liraglutide, are cornerstones in antidiabetic therapy, which also have shown positive effects in reducing BP and CVD mortality (Helmstadter et al. 2020; Pi-Sunyer et al. 2015; Mingrone et al. 2015). Liraglutide is currently available also as weight-loss medication in obese patients without diabetes and has promising effects improving hypertension and cardiovascular risk profile over 1-year treatment (Pi-Sunyer et al. 2015; Fonseca et al. 2014; le Roux et al. 2017).

Bariatric surgery has a sustained effect on weight loss, which is superior to pharmacological and lifestyle modifications. Considerable weight loss after bariatric surgery corresponds to high rates of remission of hypertension (Pareek et al. 2019). The GATEWAY trial showed that a reduction of $\geq$30% of the total number of antihypertensive medications while maintaining controlled blood pressure occurred in 83.7% of the patients randomized to receive the Roux-en-Y gastric bypass plus

antihypertensive medical therapy compared with only 12.8% patients from the control group with pharmacological therapy alone. Indeed, remission of hypertension was present in almost 50% of patients randomized to gastric bypass, whereas no patient randomized to control therapy was free of antihypertensive drugs at 12-month follow-up (Schiavon et al. 2018).

2.4 Regular Physical Activity

Epidemiological studies suggest that regular aerobic physical activity is beneficial for both reducing BP and decreasing CVD event rates and mortality (Franklin et al. 2020; Williams et al. 2018). As a result and along with the notion that "more exercise is better," more and more normotensive and hypertensive adults have increased their participation in high-intensity interval training or competitive long distance endurance events. However, the quality and intensity of the physical activity is very important. Recent evidence suggests that beyond a safe upper limit, exercise may result in deleterious cardiovascular adaptations. For instance, exercise-induced hypertension and the race distances may contribute to the occurrence of myocardial fibrosis detectable by MRI in asymptomatic triathletes (Tahir et al. 2018).

Aerobic endurance training, dynamic resistance training, and isometric training reduce resting systolic BP and diastolic BP by mean 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg, respectively, in general populations. Regular physical activity of lower intensity and duration lowers BP less than moderate- or high-intensity training, but is associated with at least a 15% decrease in mortality in cohort studies (Rossi et al. 2012). Thus, the current ESC/EHS Guidelines recommend at least 30 min of moderate dynamic exercise (walking, jogging, cycling, or swimming) on 5–7 days per week (Williams et al. 2018). The impact of isometric exercises on BP and CVD risk is less well-established, although it can be part of a comprehensive treatment regimen (Chrysant 2010).

3 Pharmacological Therapy for the Treatment of Arterial Hypertension

Current evidence suggests that treatment and gradual control of hypertension by the use of the major classes of antihypertensive drugs exert positive effects on atherosclerosis. Randomized controlled trials provided robust evidence that five drug classes lower BP and prevent CVD events. They are therefore recommended by the 2018 ESC/ESH Guidelines (Williams et al. 2018) for the treatment of hypertension: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like diuretics such as chlorthalidone and indapamide). ACE-I or ARBs alone or in combination with a calcium antagonist or a diuretic (thiazide-like to be preferred to thiazide) are considered for the first-line treatment. The use of beta-blockers is limited to special indications.

3.1 Who Should Be Treated with Pharmacological Therapy?

The benefits of antihypertensive therapy are clear in the majority of patients with arterial hypertension, but still controversial in subgroups. They include patients with Grade 1 hypertension but without manifest CVD, patients with white coat or masked hypertension and low cardiovascular risk, patients with an estimated 10-year cardiovascular risk <10%, and patients older than 75 years of age who are non-ambulatory or living in nursing homes.

Randomized trials demonstrated that treating hypertension with any antihypertensive therapy reduces cardiovascular morbidity and mortality. According to the ESC/ESH Guidelines, antihypertensive drug therapy should be initiated without any delay in patients with hypertension Grades 2 or 3 or after some time under non-pharmacological therapy in individuals with very high cardiovascular risk and Grade 1 or high-normal BP (Fig. 1). The decision to initiate drug therapy should be individualized and involve shared decision-making between patient and provider.

3.2 Choice of Initial Antihypertensive Agents

Multiple studies and meta-analyses conclude that the degree of BP reduction rather than the kind of antihypertensive medication is the major determinant of reduction in cardiovascular risk in patients with hypertension (Ettehad et al. 2016).

However, not all antihypertensive drugs are equally effective in reducing cardiovascular events and only few reduced mortality (van Vark et al. 2012).

Recommendations for the use of specific classes of antihypertensive medications are based upon clinical trial evidence of decreased cardiovascular risk, BP-lowering efficacy, safety, and tolerability. Most patients with hypertension will require more than one BP medication to reach their BP goal. As the consequence, the new guideline for treatment of hypertension suggests to use combination therapy at early stage and, if possible, a fixed-dose single-pill combination medication to improve adherence (Williams et al. 2018). Having multiple available classes of BP medications, practitioners and clinicians can individualize therapy based upon individual patient characteristics and preferences.

The following drugs are suggested for the start of monotherapy or combination therapy of arterial hypertension:

- ACE inhibitors
- ARBs
- Long-acting CCBs (most often a dihydropyridine such as amlodipine)
- Thiazide-like or thiazide-type diuretics

The previous 2013 Guidelines (Mancia et al. 2013) favored monotherapy for the start of treating hypertension. However, only a minority of patients reach the target blood pressure level under monotherapy, and the combination of two drugs is much more efficient than increasing the dose of a single drug (Williams et al. 2018).

Therefore, the current 2018 Guidelines limit the start of monotherapy to low-risk patients with stage 1 hypertension whose SBP is <150 mmHg, very high-risk patients with high-normal BP, or frail older patients; see Table 1.

3.3 Combination Therapy

Single-agent therapy will not adequately control BP in most patients whose baseline systolic BP is 15 mmHg or more above their goal. Combination therapy with drugs from different classes has a substantially greater BP-lowering effect than doubling the dose of a single agent (Wald et al. 2009).

When more than one agent is needed to control BP, a therapy with a long-acting ACE inhibitor or ARB in combination (fix if this is possible) with a long-acting dihydropyridine CCB or a diuretic is the first choice. Combination of an ACE inhibitor or ARBs with a thiazide diuretic is considered less beneficial, when hydrochlorothiazide instead of thiazide-like diuretic (chlorthalidone or indapamide) is used (Burnier et al. 2019; Williams et al. 2018). ACE inhibitors and ARBs should **not** be used together.

Chlorthalidone and indapamide have been used in several RCTs showing cardiovascular benefits, and these agents are more potent per milligram in lowering BP and have a longer duration of action compared with hydrochlorothiazide without any evidence of more side effects (Williams et al. 2018).

As such, even if head-to-head RCTs are missing, this data suggests that thiazide-like diuretics such as chlorthalidone and indapamide should be preferred over classical thiazide diuretics (e.g., hydrochlorothiazide and bendrofluazide) (Williams et al. 2018; Burnier et al. 2019; Roush et al. 2015).

The Danish Cancer Registry and the Danish Prescription Registry examined the association between the use of hydrochlorothiazide (HCTZ) and the risk of basal cell carcinoma, squamous cell carcinoma, and nodular melanoma (Pedersen et al. 2018a, 2018b, 2019). These two case-control studies showed that high cumulative doses of HCTZ (>50 g) are associated with a dose-dependent increase in the risk of non-melanoma skin cancer, but not of melanoma. The increase of risk was only small for squamous cell carcinoma and negligible for basal cell carcinoma. These studies have several limitations including the investigation of a pale-skinned population and the lack of information on genetic predisposition, sun habits, and ultraviolet exposure. Moreover, the risk reduction of death due to lower BP by HCTZ was much stronger than the small risk increase for squamous cell carcinoma by HCTZ. In general, statistically significant associations from observational studies do not prove any causal relationship.

The next step is the combination of RAAS blocker, Ca antagonists, and thiazide/thiazide-like diuretics.

If BP is not sufficiently controlled by this triple combination therapy, a mineralocorticoid receptor (MR) antagonist (i.e., spironolactone or eplerenone) may be added (Williams et al. 2015).

In patients with difficult-to-treat/resistant hypertension, a beta-blocker, an alpha-blocker, or a direct arterial vasodilator could be added.

Generally, concomitant use of beta-blockers and non-dihydropyridine CCBs should be avoided, as both drug classes reduce heart rate.

3.4 Direct Effects of Antihypertensive Drugs on Atherosclerosis

Apart from lowering blood pressure and thereby removing an important risk factor, some antihypertensive drugs appear to exert direct effects on vascular cells that are involved in the pathogenesis of atherosclerosis.

3.4.1 ARBs and ACE Inhibitors

ARBs and ACE inhibitors directly affect the renin-angiotensin-aldosterone system (RAAS), by blocking the binding of angiotensin II (Ang II) to the AT1 receptor and decreasing the production of Ang II, respectively. Hypertension promotes and accelerates the atherothrombotic process via inflammatory mechanisms linked to activation of oxidative stress by Ang II, which subsequently leads to endothelial dysfunction and development of atherogenic lesions and plaques. Endothelial dysfunction is observed in the early stages of atherosclerosis. A healthy endothelium induces vasodilatation and has antioxidant and anti-thrombotic effects. The dysfunctional endothelium releases less of nitric oxide (NO) and other protective molecules, has a disrupted redox balance, and acquires pro-constrictive and pro-thrombotic phenotypes (Flammer et al. 2012; Sudano et al. 2011). A dysfunctional endothelium has been associated with cardiovascular risk factors including diabetes mellitus or impaired glucose metabolism, hypertension, cigarette smoking, dyslipidemia, obesity, and/or metabolic syndrome (Flammer et al. 2012; Sudano et al. 2011).

RAAS antagonists, as well as some dihydropyridine CCBs, possess ancillary and synergistic effects that increase NO bioavailability, reduce oxidative stress, and suppress inflammatory responses, thereby improving both endothelial activity and vascular function (Safar and Smulyan 2007; Sudano et al. 2011; Taddei et al. 2002).

3.4.2 Diuretics

Among the diuretics, thiazide-like diuretics such chlorthalidone and indapamide but not hydrochlorothiazide were found to improve endothelial function (Dell'Omo et al. 2005; Vinereanu et al. 2014). Indapamide also reduces arterial stiffness (Agnoletti et al. 2013).

3.4.3 Calcium Antagonists

Dihydropyridine CCBs lower BP mainly through vasodilation and reduction of peripheral resistance. Several clinical studies have demonstrated that they have clinical benefits in patients with CVD. Some studies have indicated that dihydropyridine CCBs have anti-atherogenic effects beyond their BP-lowering effects (Silva et al. 2019; Sudano et al. 2011). In fact, in several animal models, dihydropyridine CCBs were found to suppress the formation of atherosclerotic

lesions. It is well-known that the production of reactive oxygen species (ROS) is involved in the progression of atherosclerosis by stimulating the production of inflammatory factors such as chemokines, cytokines, and adhesion molecules (Mason 2002; Ishii et al. 2012). Dihydropyridine CCBs can suppress ROS generation and subsequent inflammatory actions in vascular cells and arterial walls. Furthermore, several reports have revealed that dihydropyridine CCBs suppress the expression of adhesion molecules, thereby inhibiting monocyte adhesion to endothelial cells, which is an early step in the pathogenesis of atherosclerosis. Dihydropyridine CCBs also suppress proliferation and migration of smooth muscle cells both in vitro and in vivo (Mason 2002; Ishii et al. 2012). In macrophages, dihydropyridine CCBs decrease cholesterol accumulation and intracellular cholesterol esterification and increase cholesteryl ester hydrolysis. Moreover, dihydropyridine CCBs suppress the expression of matrix metalloproteinases, which affects the stability of atheromatous plaques. Interestingly, recent studies have revealed that the anti-atherosclerotic effects of dihydropyridine CCBs are mediated, at least in part, via the activation of peroxisome proliferator-activated receptor-γ (Ishii et al. 2012).

3.4.4 Beta-Blockers

In general, beta-blockers usually do not have any effect on endothelial function and atherothrombosis. The only exception is nebivolol, thanks to its high selectivity as beta1-blocker. Nebivolol inhibits the proliferation of human coronary smooth muscle and endothelial cells (Brehm et al. 2001). The specific vasorelaxant properties of nebivolol are mediated by endothelium-dependent NO release and antioxidant activity (do Vale et al. 2018). Unfortunately, nebivolol treatment in patients with non-obstructive coronary artery disease was associated with greater plaque progression and constrictive remodeling as compared to atenolol (Hung et al. 2016). Carvedilol, a nonselective blocker with additional adrenergic receptor antagonist activity, has also been shown to exert beneficial actions against endothelial dysfunction through its antioxidant effects (Bank et al. 2007), although the molecular mechanisms have not yet been fully clarified (Virdis et al. 2011).

3.4.5 Mineralocorticoid Receptor Antagonists

The MR antagonists, spironolactone and eplerenone, have been shown to reduce morbidity and mortality, in part, by blunting the adverse effects of aldosterone on endothelial function and inflammation involved in the development and complications of atherosclerosis. Recent evidence highlight that pharmacological blockade or genetic deletion of endothelial MR blunt vascular inflammation including expression of adhesion molecules, leukocyte-endothelial interactions, and plaque inflammation. Of note, in preclinical studies endothelial MR inhibition is protective only in male, but not in female mice (Moss et al. 2019). Thus, gender- and sex-specific actions of the MR in vascular function and atherosclerosis, so far still poorly investigated, will deserve future attention also in the clinical setting (Shen et al. 2017). Sympathetic hyperactivity with rising catecholamine levels and adrenergic receptors stimulation is a common feature of many CVDs, including

hypertension. This is associated with endothelial NO synthase uncoupling and a pro-constrictive vascular phenotype on adjacent small arterial vessel wall components, such as smooth muscle and endothelial cells. Activation of MR signaling in the perivascular adipose tissue surrounding small arteries contributes to β-adrenoceptor overstimulation. Thus, MR antagonists targeting the endothelium and the perivascular adipocytes surrounding small arteries may achieve a dual benefit in hypertension with involvement of sympathetic over-activation, as, for instance, in overweight and obesity (Victorio et al. 2016).

4 Perspectives of Future Antihypertensive Therapy

4.1 Unresolved Medical Needs

Despite large evidence confirming the importance of lowering BP and the availability of many effective and well-tolerated antihypertensive drugs, BP control rate is unfortunately not as high as it should. This is, at least in part, related to poor adherence to lifelong antihypertensive therapy but also, in a minority of patients, due to "difficult to treat" or "resistant" hypertension.

According to the guidelines, resistant or difficult-to-treat hypertension is defined as: *blood pressure that is not controlled to goal despite adherence to an appropriate regimen of three antihypertensive drugs of different classes (including a diuretic) in which all drugs are prescribed at suitable antihypertensive doses* (Williams et al. 2018). Pseudo-resistance as well as secondary causes of hypertension should be excluded before this diagnosis is made.

Pseudo-resistance results from some or all of the following (Williams et al. 2018):

- Inaccurate blood pressure measurement (e.g., use of an inappropriately small blood pressure cuff, not allowing a patient to rest quietly before taking readings)
- Poor adherence to blood pressure medications
- Poor adherence to lifestyle and dietary approaches to lower blood pressure
- Suboptimal antihypertensive therapy, due either to inadequate doses, an inappropriate drug combination, or exclusion of a diuretic from the antihypertensive regimen
- White coat hypertension
- Extracellular volume expansion
- Increased sympathetic activation
- Ingestion of substances that can elevate the blood pressure, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or stimulants
- Secondary or contributing causes of hypertension

4.2 New Drug Developments

Recent research has not yielded major advances in treatment of hypertension: no new targets were identified for development of antihypertensive drugs. In fact, trends show a dramatic slowing of research and development for novel blood pressure-lowering drugs. The reasons are manifold: the field is crowded with relatively effective drugs; there is a lack of major new discoveries and targets; and there are many challenges in developing blockbuster drugs. A short look in clinicaltrial.gov shows that while the development of new classes of antihypertensive drugs is apparently waning, the most current activities by big pharmaceutical companies focused on developing new combination pills, including fixed-dose combination drugs with the exception of a new ARB (fimasartan) and the compound AGSCT101, which is actually tested versus carvedilol. Fimasartan is an Ang II receptor antagonist with selectivity for the AT-1 receptor subtype, developed in 2012 by a Korean company (Boryung Pharmaceutical) as an oral antihypertensive drug (Fimasartan 2011; Chi et al. 2011). Fimasartan reduced BP with a good tolerability profile in a large-scale observational population study – Safe-KanArb (Park et al. 2013). The K-MetS study (Park et al. 2017) included 10,601 patients with metabolic syndrome and evaluated long-term effects of fimasartan on major adverse cardiovascular outcomes.

A recent study evaluated the effects of fimasartan and amlodipine therapy on carotid atherosclerotic plaque inflammation using 18F-fluorodeoxyglucose positron emission tomography imaging. Both drugs similarly decreased carotid atherosclerotic plaque inflammation in patients with acute coronary syndrome (Oh et al. 2019).

Concerning AGSCT101, a new antihypertensive drug developed by Ahn-Gook Pharmaceuticals Co., Ltd., the details are scarce. The Phase III Clinical Trial to Evaluate the Antihypertensive Effect of AGSCT101 Versus Carvedilol in Patient with Stage 1 to 2 Essential Hypertension is described in clinicaltrial.gov. Unfortunately, data about mechanism of action of this drug and status of recruiting of the described study are missing.

4.3 Device Therapy

Various device-based therapies such as renal denervation, carotid baroreceptor stimulation, creation of an arteriovenous fistula, or endovascular carotid body modification have emerged, principally targeted at the treatment of resistant hypertension.

Most data are available for renal denervation. The principle of renal denervation is to destroy some of the sympathetic nerves around the renal artery leading to lower sympathetic nervous activity and lower BP. The first results on renal denervation were obtained with devices using radiofrequency application in the open label SY MPLICITY HTN-1 and SYMPLICITY HTN-2 trials, along with several case series and observational studies. The SYMPLICITY HTN-3 trial proved safety, but was unable to show efficacy of renal denervation using a radiofrequency catheter when

compared with sham treatment in patients with severe resistant hypertension on multiple medications (Williams et al. 2018). Post hoc analyses of the SYMPLICITY HTN-3, however, revealed important information concerning patient selection, difference in adherence to antihypertensive medication in the treatment groups, a higher use of antihypertensive drugs in the sham group, as well as technical failure in performing renal denervation, which led to a revision of renal denervation technology and technique. Based on this background, several novel, sham-controlled studies have been conducted and are, in part, published. SPYRAL HTN-OFF MED (Townsend et al. 2017; Bohm et al. 2020), SPYRAL HTN-ON MED (Kandzari et al. 2018), as well as RADIANCE-HTN SOLO (Azizi et al. 2018) showed significant and consistent reductions in BP, both office and ambulatory, in patients with and without concomitant antihypertensive.

The SPYRAL HTN-ON MED was recently published and showed the superiority of catheter-based renal denervation compared with a sham procedure to safely lower BP in the absence of antihypertensive medications (Bohm et al. 2020). Catheter-based renal denervation is superior to a sham procedure to safely lower BP in the absence of antihypertensive medications.

Less data are available about the effect of carotid baroreceptor stimulation and endovascular carotid body modification both techniques aiming to reduce BP through reduction of sympathetic tone and obtained by creation of an arteriovenous fistula. Concerning carotid baroreceptor stimulation, the first-generation device reduced BP in controlled and uncontrolled clinical trials, while controlled clinical trials proving efficacy in BP reduction do not exist for the currently available second-generation carotid sinus stimulator (Jordan et al. 2019; Heusser et al. 2020).

Some, mostly uncontrolled, studies suggest that other techniques such as baroreflex amplification and carotid body modulation may lead to reduction of BP in patients with difficult-to-treat hypertension. However more evidence on safety and efficacy from ongoing large randomized sham-controlled trials is needed before baroreflex amplification and carotid body modulation can be implemented in routine clinical practice (Groenland and Spiering 2020).

Last, but not least, the possibility to safely reduce BP in patients with uncontrolled hypertension by creating a central iliac arteriovenous anastomosis was tested. The ROX CONTROL HTN study (Lobo et al. 2015) tested this hypothesis using the novel arteriovenous ROX Coupler (ROX Medical, San Clemente, CA, USA).

This small study (44 patients treated and 39 patients in the standard of care group) enrolled and showed that creation of an arteriovenous anastomosis was associated with significantly reduced BP.

The actual ESC/ESH Guidelines do not recommend the use of any device-based therapies for the routine treatment of hypertension, unless in the context of clinical studies and RCTs (Williams et al. 2018).

Nevertheless, device-based therapy for hypertension is a fast-moving field, and new data especially data from study evaluating renal denervation are expected in the near future and could change this recommendation.

5 Conclusion

Hypertension represents one of the most important modifiable risk factors for stroke, heart failure, myocardial infarction, and chronic kidney disease, contributing significantly to the global burden of CVD.

The initial assessment of a patient with hypertension is essential for choosing effective therapy. All cardiovascular risk factors as well as hypertension-mediated target organ damage and presence of comorbidities should be taken into account.

The treatment of hypertension should focus on the overall health of the patient, focusing on reducing the risk of future cardiovascular events.

For a long-lasting adherence, it is important that patients are actively involved in the process of choosing the best BP-lowering strategies.

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